

Japanese Kokai Patent Application No. Hei 4[1992]-300833

JP 04-300833

Translated from Japanese by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

Code: 5000-72137

JAPANESE PATENT OFFICE
PATENT JOURNAL
KOKAI PATENT APPLICATION NO. HEI 4[1992]-300833

Technical Disclosure Section

| | |
|------------------------------|--|
| Int. Cl. ⁵ : | A 61 K 31/557 9/107 9/12 31/557 A 61 K31/557 |
| Sequence No. for Office Use: | 7252-4C 7329-4C 7329-4C |
| Application No.: | Hei 3[1991]-93108 |
| Application Date: | March 29, 1991 |
| Publication Date: | October 23, 1992 |
| No. of Claims: | 1 (Total of 5 pages) |
| Examination Request: | Not requested |

PROSTAGLANDIN E₁-CONTAINING FATTY EMULSION SPRAY

| | |
|------------|--|
| Inventors: | Yasunori Sekiyama, c/o Green Cross Corp., Miyakojima Plant, 3-5-44 Miyakojimanaka-dori, Miyakojima-ku, Osaka-shi |
| | Asami Takada, c/o Green Cross Corp., Miyakojima Plant, 3-5-44 Miyakojimanaka-dori, Miyakojima-ku, Osaka-shi |
| | Kiichiro Nabeta, c/o Green Cross Corp., Tokyo Branch Office, 6-14 Sanban-cho, Chiyoda-ku, Tokyo-to |

Applicant:

000137764
Green Cross Corp., 1-3-3 Imabashi,
Chuo-ku, Osaka-shi, Osaka-fu

Agent:

Hajime Takashima,
patent attorney

Abstract

Constitution

A topical application spray comprising a fatty emulsion containing at least one kind of compound selected from prostaglandin E₁ and its derivatives.

Effect

The spray of this invention comprising a fatty emulsion containing PGE₁ or its derivatives is a topical application medical drug formulation with high pharmacological effects expected with only a small amount of spraying. Furthermore, the spray of this invention is directly applicable without touching diseased sites, and in addition, various kinds of treatments are possible depending on the state of the diseased sites. The formulation of this invention having said many advantages is usable against various diseases such as burns, skin ulcers, bedsores, alopecia, etc., and the administration is extremely easy and effective.

Claims

1. A topical application spray characterized by comprising a fatty emulsion containing at least one kind of compound selected from prostaglandin E₁ and its derivatives.

Detailed explanation of the invention

[0001]

Industrial application field

This invention pertains to a spray of prostaglandin E₁ and its derivatives (called PGE₁ compounds, below). In particular, it pertains to a topical application spray making it possible to apply a fatty emulsion containing PGE₁ compounds to a diseased site in the form of a mist.

[0002]

Prior art

PGE₁ compounds are present in the body in trace amounts, have various physiological actions such as blood vessel dilating action, angiogenesis action, platelet agglutination inhibitory action, epithelial regeneration promoting action, etc., and injection formulations have been made commercially available as a drug for treating peripheral blood disorders. If PGE₁ compounds were usable as a topical application drug, the treatments for bedsores, alopecia, sensitivity to cold, stiff shoulder, etc., by the vasodilating action; burns, etc., by the epithelial regeneration action and angiogenesis action; and skin ulcers, etc., by the vasodilating action and platelet agglutination inhibitory action could be carried out easily and effectively as a topical and intensive treatment without any systemic adverse effects. Therefore, it has been desirable to carry out the development of a practical formulation.

[0003]

The previous topical application drugs have been generally ointments or creams, but those PGE₁ compounds are unstable in such a formulation, and furthermore, in the case of application of such a topical application formulation to the skin surface, which is a treatment site, there are problems such as the topical application drug being physiologically incompatible with the skin surface, application of the topical application drug being painful, damage being caused on the newly generated skin surface, etc., and actually prolonging the condition in many cases.

[0004]

Incidentally, PGE₁ compounds are chemically unstable, but a formulation has been proposed to stabilize them by allowing a fatty emulsion to contain them and using it as an injection formulation. This fatty emulsion is a low-viscosity fluid enabling administration by injection but as it is, being difficult to administer effectively as a topical application drug.

[0005]

Problems to be solved by the invention

Therefore, the object of this invention is to provide a formulation enabling effective topical application administration of PGE₁ compounds. Especially, the object of this invention is to provide a topical application formulation of PGE₁ compounds making it possible to maintain chemical stability of the PGE₁ compounds, which is physiologically compatible to the skin surface without causing any pain to patients and without damaging newly generated skin, etc.

[0006]

Means to solve the problems

To accomplish the above objective, the inventors of this invention studied diligently; as a result, they found that the above objective could be accomplished by preparing a spray formulation of a fatty emulsion containing PGE₁ compounds, and they arrived at this invention. Specifically, the topical application drug of this invention is characterized by comprising a fatty emulsion containing at least one kind of compound selected from the PGE₁ compounds.

[0007]

The PGE₁ compounds of this invention are not especially restricted as long as they have a PGE₁ activity, and they may be derivatives having a higher lipophilicity than that of PGE₁. Specific examples of such PGE₁ compounds are PGE₁, PGE₁ alkyl ester (Japanese Kokai Patent Application No. Sho 59[1984]-216820), PGE₁ alkoxycarbonylalkyl ester or PGE₁ acyloxyalkyl ester (Japanese Kokai Patent Application No. Sho 59[1984]-206399), 7-thia-PGE₁ (Japanese Kokai Patent Application No. Sho 58[1983]-110562), etc.

[0008]

The fatty emulsion of this invention suitably comprises mainly 5-50% soybean oil, 1-50 parts by weight (preferably 5-30 parts by weight) of phospholipids per 100 parts by weight soybean oil, and a suitable amount of water. In addition, it is also possible to add, if necessary, an emulsifying agent (fatty acid having 6-22 carbon atoms, preferably 12-20 carbon atoms or its physiologically acceptable salt in the amount up to 0.3% (w/v)); stabilizer (cholesterol in the amount of 0.5% (w/v) or less, preferably 0.1% (w/v) or less, or phosphatidic acid in the amount of 5% (w/v) or less, preferably 1% (w/v)); a polymeric substance (such as dextran, vinyl polymer, nonionic surfactant, gelatin or hydroxyethyl starch in the amount of 0.1-5 parts by weight (preferably 0.5-1 part by weight) per 1 part by weight of sterol); or an isotonic agent (such as glycerol or glucose).

[0009]

The content of PGE₁ in a fatty emulsion is suitably adjustable depending on the form of the fatty emulsion and applications, but in general, it is in the range of 0.1-500 µg/mL, preferably 1-100 µg/mL of the fatty emulsion. Soybean oil usable for preparing the fatty emulsion is a highly purified soybean oil which is a highly purified oil (purity of 99.9% or higher containing triglycerides, diglycerides and monoglycerides) prepared by carrying out, for example, steam distillation of a purified soybean oil.

[0010]

Phospholipids that are usable are purified phospholipids such as egg yolk lecithin, soybean oil lecithin, etc., which can be prepared by carrying out conventional fractionation using an organic solvent. For example, raw egg yolk lecithin phospholipids are dissolved in a cold mixture of n-hexane and acetone; acetone is gradually added while stirring; the insoluble precipitates formed are recovered by filtration, and after the procedures are repeated once more, the solvent is distilled off to obtain purified phospholipids. The product prepared comprises mostly phosphatidylcholine and phosphatidylethanolamine as well as other phospholipids such as phosphatidylinositol, phosphatidylserine, sphingomyelin, etc. Furthermore, if necessary, phospholipids may be purified further by using a chromatographic column to isolate a composition containing mostly phosphatidylcholine which may be used as phospholipids in this invention.

[0011]

As the fatty acid having 6-22 carbon atoms used as an emulsifying agent, any of those usable in medical drugs can be used. It may be a straight-chain or branched fatty acid, and preferable specific examples include straight-chain stearic acid, oleic acid, linolic acid, palmitic acid, linoleic acid, myristic acid, etc. Their physiologically allowable salts, such as alkali metal salts (sodium salts, potassium salts, etc.), alkaline-earth metal salts (calcium salts, etc.), etc., are also usable.

[0012]

As a cholesterol or phosphotidic acid usable as a stabilizer, any of those usable for medical drugs is usable. As a vinyl polymer used for the polymeric substance of this invention, there are poly(vinylpyrrolidone), poly(vinyl alcohol), etc. Furthermore, as a nonionic surfactant, there are polyalkylene glycols (such as polyethylene glycol having a mean molecular weight of 1000-10,000, preferably 4000-6000), polyoxyalkylene copolymers (such as polyoxyethylene-polyoxypropylene copolymer having a mean molecular weight of 1000-20,000, preferably 6000-10,000), hardened castor oil polyoxyalkylene derivatives (such as hardened castor oil polyoxyethylene-(20)-ether, hardened castor oil polyoxyethylene-(40)-ether, hardened castor oil polyoxyethylene-(100)-ether, etc.), castor oil polyoxyalkylene derivatives (such as castor oil polyoxyethylene-(20)-ether, castor oil polyoxyethylene-(40)-ether, castor oil polyoxyethylene-(100)-ether, etc.), etc.

[0013]

The optimal composition for the fatty emulsion of this invention is, for example, as follows.

| | |
|----------------------------|-----------------|
| PGE ₁ compounds | 1-100 µg |
| Purified soy bean oil | 5-500 mg |
| Highly purified lecithin | 5-50 mg |
| Concentrated glycerol | 5-50 mg |
| Distilled water | Suitable amount |
| Total | 1 mL |

[0014]

The fatty emulsion of this invention is prepared, for example, by using the following method. Specifically, the required amounts of PGE₁ compounds, soybean oil, phospholipids and other additives described above are mixed and heated to obtain a dissolved mixture which is subsequently treated for homogenization in a conventionally used homogenizer (such as high-pressure jet-type homogenizer, ultrasonic homogenizer, etc.), to obtain an oil-in-water dispersion. Subsequently, a necessary amount of water is added; the mixture is treated again for homogenization in the above homogenizer to obtain a water-in-oil emulsion. If necessary, additives such as stabilizers, isotonic agents, etc., may be added after the fatty emulsion is formed (Japanese Kokai Patent Application No. Sho 58[1983]-222014).

[0015]

The topical application spray of this invention is prepared as a topical application spray comprising the fatty emulsion prepared as described above alone or with known additives added.

[0016]

The topical application spray of this invention is preferably packed in a sprayer container having a structure with the following features 1-5.

1. It has a jet-flow opening.
2. No reverse flow of air into the container.
3. The container is a sealed container.
4. The volume of the container is variable depending on the volume of the emulsion. Namely, as the emulsion is used, the volume of the container is reduced as much as the volume of the emulsion used forming no empty space inside the container.
5. The emulsion is sprayed from the jet-flow opening by mechanical pressure. Namely, the spraying is carried out mechanically instead of using the pressure of a propellant, etc.

[0017]

As a sprayer container satisfying the above conditions, there is a commercially available "Airless Pump for Drug Administration" (Top K.K.), but it [the invention] is not necessarily limited to it.

[0018]

By filling a sealed container such as the one described above, the PGE₁ compounds and lecithin are prevented from oxidation by air, and the stability of the emulsion can be maintained at the same level as that at the time of packing the emulsion in the container. Furthermore, the emulsion inside is not contaminated by airborne bacteria because there is no backflow of air into the container.

[0019]

As a specific application method of the topical application spray of this invention, there are, for example, direct spraying to a diseased site, spraying and subsequent rubbing in, spraying onto gauze or a sheet material and attaching it on a diseased site, etc.

[0020]

The dose of the drug formulation of this invention is variable depending on the state of disease, size of diseased sites, etc., but in general, the dose of PGE₁ compounds is in the range of about 1 ng/kg of bodyweight to 10 mg/kg of bodyweight. Furthermore, the dose is applied to a diseased site once to several times a day.

[0021]

Application example

This invention is explained in specific detail by using experimental and application examples as follows, but this invention is not at all restricted by these examples.

Example 1

Test for stability of PGE₁-containing fatty emulsion spray over time

A drug administration airless pump (Top K.K.) was filled in a sterile manner with a spray formulation comprising 7 mL of a PGE₁-containing fatty emulsion prepared in Application Example 1, and the amount of liquid sprayed, appearance, pH, peroxide, free fatty acid, emulsion particle size and PGE₁ content residual rate were evaluated over time. The results obtained are shown in Table I (storage by refrigeration).

[0022]

Table 1

| | | (2) | (3) | (4) | (5) |
|------|----------------------------|------|------|------|------|
| (1) | 測定項目 | 充填直後 | 1ヵ月後 | 3ヵ月後 | 6ヵ月後 |
| (6) | 総噴霧液量 (ml) (30回噴霧量) | 2.8 | 2.7 | 3.0 | 2.9 |
| (7) | 外観 (肉眼観察) | 異常なし | 異常なし | 異常なし | 異常なし |
| | pH | 5.72 | 5.73 | 5.76 | 5.76 |
| (9) | 過酸化物 (mEq/l) | 0.02 | 0.21 | 0.18 | 0.20 |
| (10) | 遊離脂肪酸 (mEq/l) | 8.33 | 9.70 | 8.78 | 9.67 |
| (11) | 乳剤粒子径 (nm) | 223 | 251 | 223 | 220 |
| (12) | PGE ₁ 含量残存率 (%) | 100 | 96 | 94 | 93 |

- Key:
- 1 Measurement item
 - 2 Immediately after filling
 - 3 After 1 month
 - 4 After 3 months
 - 5 After 6 months
 - 6 Amount of liquid sprayed (after 30 times spraying)
 - 7 Appearance (naked eye observation)
 - 8 No abnormality
 - 9 Peroxide (mEq/L)
 - 10 Free fatty acid (mEq/L)
 - 11 Emulsion particle size (nm)
 - 12 PGE₁ content residual rate (%)

[0023]

As is apparent from the results shown above, the formulation of this invention was found to have excellent stability.

[0024]

Experimental Example 2

Sterility test at the time of long-term storage of PGE₁-containing fatty emulsion spray

The sterility test of the general test method "Sterility test, direct method" of Pharmacopoeia Japonica was carried out for the residual liquid when a drug administration airless pump (Top K.K.) was filled in a sterile manner with the spray of Experimental Example 1 and sprayed periodically. The results on the number of samples with microbiological growth/number of samples tested are shown in Table II.

[0025]

Table 2

| ① 測定項目 | | ② 充填直後 | ③ 1ヵ月後 | ④ 6ヵ月後 |
|--------|------|--------|--------|--------|
| ⑤ 無菌試験 | ⑥ 細菌 | 0 / 3 | 0 / 3 | 0 / 3 |
| | ⑦ 真菌 | 0 / 3 | 0 / 3 | 0 / 3 |

Key: 1 Measurement item
 2 Immediately after packing
 3 After 1 month
 4 After 6 months
 5 Sterility test
 6 Bacterium
 7 Fungus

[0026]

As is apparent from the results shown, microbiological contamination was found to be preventable.

[0027]

Application Example 1

To 100 g of purified soybean oil, 50 mg PGE₁, 20 g purified egg yolk lecithin and 2.4 g oleic acid were added and dissolved or dispersed by heating to about 50°C. Subsequently, 25 g of Japanese Pharmacopoeia glycerol and distilled water were added to make up to a total volume of 1 L, and the mixture was preliminarily emulsified by using a homomixer. The mixture was

subsequently emulsified by using a Manton-Gaulin [transliteration] homogenizer and allowing 10 passes with a first-stage pressure of 120 kg/cm² and total pressure of 500 kg/cm². As a result, a homogenized PGE₁-containing fatty emulsion having extremely microscopic particles was prepared. The mean particle size of the emulsion was found to be in the range of 0.2-0.4 μm, and there was no particle larger than 1 μm. A sprayer container comprising EO gas-sterilized nozzle and pump portion as well as dry heat-sterilized main glass body and high-pressure steam-sterilized rubber stopper was filled in a sterile manner with the prepared emulsion. The particles after spraying were found to have a size of 10 μm or larger, contain PGE₁-containing fatty emulsion, and the respective particles showed no changes such as decaying, deformation, etc.

[0028]

Application Example 2

To 100 g of purified soybean oil, 10 mg PGE₁, 18 g purified egg yolk lecithin and 1 g oleic acid were added and dissolved or dispersed by heating to about 50°C. Subsequently, 25 g Japanese Pharmacopoeia glycerol and distilled water were added to make up to a total volume of 1 L, and the mixture was preliminarily emulsified by using a homomixer. After the crude emulsification, the same procedures as those used in Application Example 1 were carried out to obtain a homogenized PGE₁-containing fatty emulsion having extremely microscopic particles. A drug administration airless pump sprayer container was filled with the emulsion prepared. Similarly to the results obtained in Application Example 1, the spray particles showed no physicochemical changes.

[0029]

Application Example 3

To 100 g of purified soybean oil, 2.5 mg PGE₁ and 18 g purified egg yolk lecithin were added and dissolved or dispersed by heating to about 50°C. Subsequently, 22 g Japanese Pharmacopoeia glycerol and distilled water were added to make up to a total volume of 1 L, and the mixture was preliminarily emulsified by using a homomixer. After the crude emulsification, the same procedures as those used in Application Example 1 were carried out to obtain a homogenized PGE₁-containing fatty emulsion having extremely fine microscopic particles. A drug administration airless pump sprayer container was filled with the emulsion prepared. Similarly to the results obtained in Application Example 1, the spray particles showed no physicochemical changes.

[0030]

Clinical Example 1

The sprayer prepared in the Application Example 1 was applied to a patient with bedsores (67-year-old female with bedsores at the ischium and sacrum) by direct spraying, and as a result, it was possible to obtain good treatment effects without causing any difficulty to the patient.

[0031]

Clinical Example 2

The spray prepared in Application Example 2 was sprayed on a sheet of collagen, which was subsequently used to treat a patient with second-degree burns (8-year-old male at the right leg). As a result, the epithelial regeneration-promoting effects were observed without causing any difficulty to the patient during the process of treatment, the burns were completely healed after 7 days, and clean skin generation was achieved.

[0032]

Effect of the invention

The PGE₁-containing fatty emulsion spray of this invention is a topical application drug formulation from which high pharmacological effects are expected with only a small amount of spraying. Furthermore, the sprayer of this invention enables direct drug administration without coming into direct contact with a diseased site, and furthermore various kinds of treatments are possible depending on the state of the diseased sites. The drug formulation of this invention having many advantages such as those described above is applicable in treating many diseases such as burns, skin ulcers, bedsores, alopecia, etc., and the administration is extremely easy and effective.